THE

AMERICAN JOURNAL

OF THE MEDICAL SCIENCES

NOVEMBER, 1916

ORIGINAL ARTICLES

THE SUSCEPTIBILITY OF MAN TO FOREIGN PROTEINS.[1]

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Throughout the literature of the last century one may find isolated statements regarding the unexpected effects upon certain individuals of substances now recognized as containing proteins, and perhaps the most significant of these are the observations of Blackley, in 1873, on the effect of grass pollens upon the nasal mucous membrane, conjunctivæ, and the scarified skin of individuals suffering from hay fever. About 1869 and 1870, when transfusions of sheep's blood were much in vogue, it was frequently noted that an urticaria appeared as a late effect of this treatment. It was not, however, until the introduction of diphtheria antitoxin in 1894 that the results of injections of foreign proteins in man received serious study. Lublinski,[2] in the year 1894, described what is now the perfectly familiar picture of serum disease as a sequel to the injection of diphtheria antitoxin, but not until the careful investigations of von Pirquet and Schick,[3] in 1905, was any important light thrown upon the process. They immediately recognized the importance which the so-called antibodies against foreign protein, in this instance horse serum, might have in the production of serum disease,

[1] Lecture delivered before the Harvey Society, New York, February 26, 1916.

[2] Deutsch. med. Wchnschr., 1894, xx, 854.

[3] Die Serumkrankheit, 1905.

and the subsequent observations and experiments by Otto, Rosenau and Anderson, Gay and Southard, Friedemann, Doerr, Friedberger and a host of others[4] have made it quite clear that the introduction of native foreign protein follows essentially the same biological and chemical physical principles in man as in the lower animals.

It is only necessary to point out here that the introduction of the long series of foreign proteins that have been subjected to experiment is followed by the production in the animal body of various antibodies which have the power to unite with the original substance or antigen to produce a new effect. This new effect may be obvious and best studied by mixing antibody and antigen outside the body, as is the case with the hemolysins, the bacterial agglutinins, bacteriolysins, and precipitins; it may be obtained both *in vitro* and *in vivo*, as is the case with antitoxin, or it may be demonstrable almost exclusively in the animal body, as is the case with anaphylaxis.

The bare outlines of the experiments from which our knowledge of anaphylaxis has been derived may be summed up in a statement of the following condition: An animal is injected subcutaneously, intraperitoneally, or intravenously with a small amount of foreign protein, for example horse serum. This produces no visible effect. If, however, after an interval of at least nine to fourteen days, a second injection of the same protein is made the animal becomes ill immediately, presenting characteristic symptoms which differ only slightly for different species; while if the dose of serum is properly gauged and made into the peritoneum or vein the animal dies within five minutes to one hour. This is known as active anaphylaxis. Second, the condition known as passive anaphylaxis, first described by Gay and Southard,[5] Otto[6] and Friedemann,[7] who showed that the blood of an animal sensitized to horse serum confers this specific sensitiveness to a normal guinea-pig. Sensitiveness develops in the normal animal after a period of fifteen to eighteen hours following the inoculation of the serum from the sensitized guinea-pig, and lasts a few days or at most weeks. It is dependent upon the presence in the blood of the actively sensitized animal of antibodies for the specific proteins which are thus transferred passively to the normal guinea-pig. This transfer may take place during pregnancy from mother to offspring. Third, the state termed anti-anaphylaxis by Besredka and Steinhardt,[8] in which for a short period following the anaphylactic shock the actively sensitized animal becomes insensitive to injections of horse serum. Following this period of anti-anaphylaxis an animal may again become sensitive to the specific protein and remain so for months or years. Finally, it was shown by Rosenau and Anderson[9] that the repeated injection of horse serum at intervals of two or three days produced a refractory condition toward subsequent injections of the specific protein, so that for a long period of time they no longer react to such an injection with anaphylactic symptoms. This refractory state, however, finally gives way to sensitiveness, and eventually the animal is again susceptible. During the refractory state, which has been called one of immunity, antibodies for horse serum may be present in great concentration in the serum, and when injected into normal guinea-pigs will passively sensitize them to the protein.

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[4] For full bibliography see: Doerr, Wassermann and Kolle, Handb. d. path. Microorg., 1913, ii, 947. Richet, L'Anaphylaxie, 1912. von Pirquet, Arch. Int. Med., 1911, vii, 259, 383. Friedemann, Jahresb. u. Immunitätsf., 1910, vi, Abst. i, 31. Besredka, Ibid., 1912, viii, 90. Vaughan, Protein Split Products in Relation to Immunity and Disease, 1913. Rosenau and Anderson, Arch. Int. Med., 1909, ii, 579. Otto, Wassermann and Kolle, Handb. d. path. Microorg., 1908, ii, 255. Auer, Forchheimer's Therapeusis, 1914, v, 39.

[5] Journal of Med. Research, 1907, xi, 143.

[6] München. med. Wchnschr., 1907, liv, 1665.

[7] Ibid., 2414.

[8] Ann. de l'Inst. Pasteur, 1907, xxi, 117, 384.

After this brief statement of the fundamental principles of anaphylaxis it is possible to consider in more detail the process as it develops in man, for the introduction of antitoxic and antibacterial sera has given ample opportunity for an exact analysis of the effect of single and repeated injections of foreign protein. This, as a rule, has been horse serum, though the serum from any foreign species will give the same results. As in an animal, so in man, primary injections of horse serum given by any route produce no immediate symptoms. In the vast majority of instances it remains, as can be shown by the presence of precipitinogen and by anaphylactic methods in the circulation, for long periods of time, and is excreted very slowly, if at all, by the kidneys. For a period of six to ten days following primary injection, known as the incubation period, there is nothing to be observed, but at any moment after the sixth day typical serum sickness may appear. (See Chart.)

The symptoms and signs of this disease are as striking and characteristic as any natural disease process with which we are familiar. Usually a skin eruption with intense itching preceded by glandular enlargement ushers in the attack. The eruption starts, as a rule, at the point of inoculation, but spreads rapidly over the entire body. Urticaria is most common, but there may be a patchy or diffuse erythema, scarlatiniform rashes, or a multiform eruption. Edema of the face and ankles is usual and may affect the entire body. In rare instances it is localized to the pharynx or larynx, and in one instance a transient hemiplegia was supposed to be caused by local edema of the meninges. The temperature is elevated, and there is general malaise and headache with prostration, though rarely nausea or vomiting. Joint pains are very common in severe cases. They are always multiple, and though the pain is exquisite on motion, there is little tenderness and no swelling or reddening.

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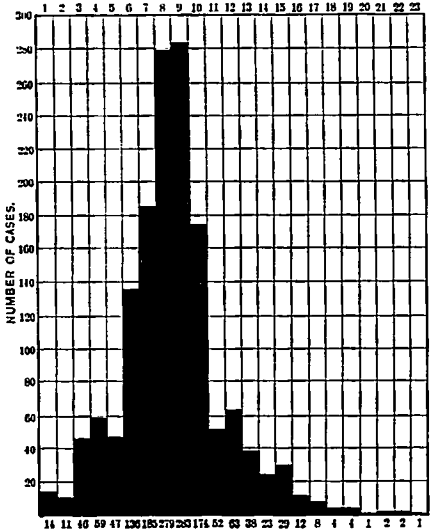
[9] Bull. 29, Hyg. Lab. U. S. P. H. and M. H. S., 1906; Bull. 36, Hyg. Lab. U. S. P. H. and M. H. S., 1907.

Quite regularly the lymph nodes are enlarged; they are often swollen to the size of walnuts in the region draining the primary injection, and may be excessively tender. The spleen is sometimes enlarged; in 5 to 9 per cent. of the cases there is albuminuria, and, as I shall point out later, there are often disturbances in the functional activity of the kidneys. Examination of the blood, according to von Pirquet, shows a primary polymorphonuclear leukocytosis with subsequent leukopenia and absolute increase in the lymphocytes. The disease may last for twenty-four hours to twenty days or longer. In the severest cases there are one to four relapses which usually occur after the use of large amounts of serum, and come; according to Axenow,[10] at ten day intervals.



Incubation period in 1493 cases of Serum Disease. Figures at top indicate number of days after injection of serum. Bottom line of figures represents number of cases.

The occurrence, intensity, and duration of the disease depend, upon several factors: First, upon the amount of serum used. The disease is not usual after small doses, but is extremely common after large ones. The statistics of Weaver,[11] based on a study of 801 reported cases, show an incidence of 10 per cent. after the injection of 1 to 10 c.c. of serum. Most of the attacks are mild, but the incidence increases in almost direct proportion to the amount of serum used, until, when quantities over 90 c.c. are employed, 75 to 100 per cent. of the patients develop serum disease. Secondly, it seems possible, from the statistics of Bokay[12] and Schulz,[13] that the incidence may depend to some extent upon the source of the serum. Apparently certain horses yield a serum which is much more likely to be attended by serum disease than others. And finally the individual characteristics of the patient play a role, for the same dose of serum from the same source may produce quite different affects in different persons.

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[10] Jahrb. f. Kinderh., 1913, lxxviii, 565.

A second injection of serum before the tenth day or before the onset of serum disease is not attended by immediate symptoms. It has already been observed that in the case of animals, repeated injections of horse serum at two- to three-day intervals produce a condition which makes them refractory to subsequent injections, which state may last many weeks. By the same method in human beings the incubation period for serum sickness may be prolonged for weeks, but its final appearance cannot always be prevented, and after these multiple doses at short intervals the attack, when it appears, is, according to Goodall,[14] especially severe. If, however, a second injection is made after the tenth day, von Pirquet and Schick have shown that the following reactions may occur: (1) The local immediate reaction. Within fifteen minutes to an hour after subcutaneous injection of serum, edema, erythema, or urticaria appears at the site of inoculation. (2) The general immediate reaction which is characterized by a more or less severe general reaction coming on within twelve to twenty-four hours after the inoculation and having the characteristics of a fulminant case of serum sickness. The most violent and general immediate reactions are accompanied by such symptoms as dyspnea of asthmatic type, cyanosis, collapse, nausea and vomiting, and suppression of urine, symptoms which are not regularly seen in the ordinary form of the disease. (3) The accelerated reaction or form in which the incubation of the serum sickness falls between the immediate reaction and the ordinary reaction and comes on within a period of three to five days after inoculation, and finally the second injection may be followed simply by the normal form of serum sickness. Any of these reactions may occur separately or may be combined in one and the same patient.

The actual occurrence of the immediate general reaction following a second injection varies according to different observers. It is noted most often, according to von Pirquet and Goodall, between the thirty-fifth and eightieth day after the primary inoculation of serum, and occurs when serum is injected in large quantities at this period in about 60 per cent. of the cases. An injection made after three months is usually followed by an accelerated reaction, and when years have elapsed the general reaction may be of the ordinary type. The immediate reaction, though it may be severe, has, as far as I know and as the statistics of Park[15] and Nemmser[16] and Cuno[17] show, never caused death when the inoculation is made subcutaneously. Following a second intravenous injection, however, Koch[18] has reported one death. After the second injection of serum made in the spinal canal, coma, convulsions, and death have been reported by Hutinel,[19] Grysez and Dupuich,[20] and Archard and Flandin.[21] Auer[22] has recently analyzed all these cases and considers that death is not due to true anaphylactic shock. The symptoms are certainly not those of a general immediate reaction, but it seems possible that a local immediate reaction may occur, similar to that in the skin which might produce extensive edema of the meninges, and in this way account for the symptoms as they are described.

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[11] Arch. Int. Med., 1909, iii, 485.
[12] Deutsch. med. Wchnschr., 1911, xxxvii, 9.
[13] Berl. klin. Wchnschr., 1914, li, 349, 401.
[14] Jour. Hyg., 1907, vii, 607; British Med. Jour., 1913, ii, 1359.

The local immediate reaction upon second injection is specific, as was shown by von Pirquet, and is analogous to the Arthus phenomenon in the rabbit. Lucas and Gay[23] describe it as a very frequent occurrence in children receiving prophylactic doses of diphtheria antitoxin at three weeks' intervals. Moss,[24] in 1910, drew attention to the value of this immediate cutaneous reaction in determining the presence of sensitiveness to horse serum in persons who had previously been injected and found that five of twenty-one such patients reacted positively to an intracutaneous injection of horse serum two to three years after the primary injection. The exact time of appearance of this immediate reaction for skin sensitiveness has been studied by Hamburger and Pollok,[25] Michaels,[26] and Cowie.[27] By making intradermic injections of 0.1 to 0.5 c.c. of serum at short intervals these observers have noted its appearance on the fifth day after the injection of serum and its persistence for years after. Michaels makes the important observation that the reaction cannot be obtained during serum sickness, and in two instances when it was possible to obtain a positive skin reaction before the onset of the disease it disappeared during the course of the serum sickness. Immediately after the serum sickness all observers agree that the skin reaction rapidly increases in intensity, and when the test is properly performed it is obtained in 80 to 90 per cent. of the cases even for years after.

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[15] Tr. Assn. Amer. Phys., 1913, xxviii, 95.

[16] Deutsch. med. Wchnschr., 1913, xxxix, 740.

[17] Ibid., 1914, xl, 1017.

[18] Berl. klin. Wchnschr., 1915, lii, 685.

[19] Presse méd., 1910, xviii, 497.

[20] Bull. et mém. Soc. méd. d. hôp. de Paris, 1912, xxxiii, 371.

[21] Compt. rend. Soc. biol., 1912, lxxiii, 419.

[22] Forchheimmer's Therapeusis, 1914, v, 39.

[23] Jour. Med. Research, 1909, xx, 251.

[24] Jour. Am. Med. Assn., 1910, lv, 776.

[25] Wien. klin. Wchnschr., 1910, xxiii, 1161.

[26] Arch. Mal. d. Enfants, 1913, xvi, 835.

[27] Am. Jour. Dis. Child., 1914, vii, 253.

Dr. Rackamann and I have employed this method to determine the development of skin sensitization in serum disease. The test dose has been very small and injected intradermally, 0.02 c.c. of pure serum and of serum in $\frac{1}{10}$ and $\frac{1}{100}$ dilutions has been employed. After these minute doses skin sensitiveness does not appear until serum disease has set in, but once having made its appearance the reaction increases in intensity and has been present by the fifteenth to twentieth day in most instances. A reaction of equal intensity has been obtained in several adults two or three years after an injection of antitoxin. The intradermal method is much the most sensitive of any of the cutaneous tests, and may be strikingly positive with serum in $\frac{1}{100}$ or $\frac{1}{500}$ dilution, although the scarification method such as used for tuberculin by von Pirquet gives a negative response with undiluted serum. It is, as far as we have observed, specific and cannot be brought about in these cases by the use of various other animal sera, egg-white, casein, or vegetable proteins. It consists in the appearance after a period of ten to fifteen minutes of an elevated, yellowish, firm wheal, surrounded by a bright red erythematous areola. This increases rapidly in size until the wheal reaches at the end of thirty to forty-five minutes 1 to 2 cm. in diameter, and the erythematous zone 3 to 6 cm. in diameter. During this period the patient often complains of itching at the site of inoculation. At the end of an hour the reaction fades and in twelve hours nothing is to be seen. Salt solution, human sera, and various other animal sera result in the formation of a minute white papule 5 to 6 mm. in diameter, about which there may appear a narrow red zone. This traumatic reaction fades in five to fifteen minutes, and is almost invisible at the end of half an hour when the true reaction is at its height. Knox, Moss, and Brown[23] have found that under similar conditions a skin reaction is obtained in the rabbit. It makes its appearance first on the eleventh day after primary inoculation of serum, and is present in most cases by the sixteenth to twenty-second day. It differs from the reaction in the human being in that the development is much slower, attaining its height only after twelve to twenty-four hours, while it persists much longer, lasting two or three days. The skin reaction must be considered as a delicate and probably specific reaction of an individual artificially sensitized to a foreign protein, and makes its appearance from five to fifteen days after the primary injection.

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[23] Jour. Exp. Med., 1910, xii, 562.

At about the time that this sensitiveness appears, and sometimes immediately before the onset of the serum disease, other reactions occur which are considered evidence of the formation of antibodies to the foreign protein. These are represented by the appearance in the blood serum of precipitins for the foreign protein and the substance which is capable of transmitting the sensitive state passively from one animal to the other. Hamburger and Moro,[29] who first demonstrated precipitins for horse serum in the blood of cases of serum disease, and Doerr and Russ,[30] as well as Weil,[31] experimenting later in animals, have attached much importance to the precipitins as a part of the anaphylactic reaction, though von Pirquet was inclined to regard the production of precipitins as an accompanying phenomenon rather than as one upon which anaphylaxis is dependent. C. Wells,[32] has followed the curve of production of these antibodies during serum sickness in children receiving diphtheria antitoxin. In some cases precipitins are demonstrable about the sixth day after injection of serum and before the sickness starts, but with the onset of serum sickness the precipitins diminish or disappear to increase rapidly after the disease to a high degree of concentration. A diminution again takes place sixteen days later, and finally the precipitins can no longer be demonstrated.

More closely related to the anaphylactic state than the precipitin is the presence of the substance which is capable of causing passive sensitization, variously designated immune substance, anaphylactic antibody, anaphylactin, or allergin. Though Doerr and Russ[33] have undertaken to measure quantitatively the amount of this antibody in a given specimen of serum, there are certain factors, as has recently been shown by Lewis,[34] which complicate such a quantitative analysis of the anaphylactic antibody, and consequently the result obtained from passive transfer can only roughly measure the actual amount of this substance in the actively sensitized animals. That there is some parallelism between the amount of precipitin and quantity of anaphylactin has been shown by Burkhardt,[35] but when several injections of serum are given to sensitize actively the two reactions do not run parallel. Weill, Hallé, and Lémaire[36] found that the blood of rabbits receiving a single injection of horse serum showed the power to transmit the anaphylactic antibodies to guinea-pigs after the lapse of ten days. This increased in intensity up to the twenty-fifth day, and gradually disappeared after the sixtieth day. When, however, repeated injections of horse serum were employed at two months' intervals the ability of the rabbits' serum to sensitize guinea-pigs appears immediately after the last injection, but does not persist as long. Anderson and Frost[37] found that the blood of guinea-pigs contained "anaphylactin" for as many as four hundred and fifty days after sensitization, and as Rosenau and Anderson originally noted, guinea-pigs made refractory to anaphylactic shock by repeated injections of horse serum, still carry in their serum anaphylactic antibodies in large amounts. Attempts to demonstrate this phenomenon in man have met often with indifferent success. Anderson and Frost,[38] as well as Archard, Flandin,[39] Weil,[40] and Yamanouche[41] report isolated successful results, but Novotny and Schick[42] obtained positive results in only 2 out of 12 cases. Gryez and Bernhard,[43] however, were more successful, and with the blood drawn from eleven children five to two hundred and thirty-four days after injection of diphtheria antitoxin were able to sensitize guinea-pigs passively to horse serum. Dr. Rackamann and I have made some observations upon the appearance of this anaphylactic antibody in ten individuals receiving horse serum. We have found that the anaphylactin was present in one or two instances before the appearance of serum disease, but in the vast majority of cases it is only demonstrable at the subsidence of the symptoms. Once having appeared at this time, however, it may persist for many days and be present in such concentration that one can readily transfer the sensitiveness from man to a guinea-pig.

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[29] Wien. klin. Wchnschr., 1903, xvi, 445.

[30] Ztschr. f. Immunitätsf., orig., 1909, iii, 181. Doerr, Wassermann and Kolle, Handb. d. path. Microörg., 1913, ii, 947.

[31] Jour. Immunol., 1916, i, 1, 19, 35, 47.

[32] Jour. Inf. Dis., 1915, xvi, 63.

[33] Loc. cit.

[34] Jour. Inf. Dis., 1915, xvii, 241.

[35] Ztschr. f. Immunitätsf., orig., 1910, viii, 87.

[36] Compt. rend. Soc. de biol., 1908, lxv, 141.

It will thus be seen that toward the end of the incubation period of serum disease, certain antibodies and immune reactions, namely, the skin reaction, the precipitin reaction and anaphylactin, can occasionally be demonstrated in the blood serum. With the appearance of the symptoms they diminish or disappear to reappear with great intensity at the subsidence of the attack. Since the serum or antigen during this entire period may still be demonstrated in the circulation, it is highly probable, as was proposed by von Pirquet, that serum disease is brought about by a union of the rapidly forming antibodies and the circulating antigen. The theoretical explanation as to the place and cause of this union has been the subject of much discussion. The union, of course, may take place in the circulating blood, thus liberating toxic substances that produce the symptoms of serum disease or anaphylaxis; second, the union may occur in the tissues and cells of the body; or, third, it may proceed in both situations. Friedberger, who has experimented extensively along this line, has advanced first one and then the other view, and in the human being the appearance of precipitins and the anaphylactic

[37] Bull. 64, Hyg. Lab. U. S. P. H. and M. H. S., 1910.

[38] Loc. cit.

[39] Loc. cit.

[40] Proc. Soc. Exp. Biol. and Med., 1914, xii, 37.

[41] Compt. rend. Soc. de biol., 1910, lxviii, 1000.

[42] Ztschr. f. Immunitätsf., orig., 1909, iii, 671.

[43] Comp. rend. Soc. de biol., 1912, lxxiii, 387.

antibodies in the blood stream before the onset of serum disease, might lead one at first to suppose that the reaction was principally in the circulating blood, as was the original idea of von Pirquet. The observations of Pearce and Eisenbrey,[44] of Schulz[45] and those of Dale,[46] which have been extensively amplified and confirmed by Weil,[47] show definitely that the cells of sensitized animals, and certainly the smooth muscle of the uterus, freed from all traces of the body fluids, are capable of reacting violently when brought in contact with the specific antigen toward which the animal is sensitive. The original observation of Rosenau and Anderson repeatedly confirmed that the blood serum of an animal made highly refractory by repeated injections of horse serum may still contain large amounts of anaphylactic antibody, is in support of the idea at present quite widely accepted that the presence of these antibodies in the serum is a source of protection rather than harm. Circulating in the blood in large quantities they unite slowly with the reinjected antigen or at least "fix" it so that the antigen as such is prevented from coming in contact with the cells of the body. The facts which have been brought out in the study of serum disease in man might be interpreted in the light of either theory.

The onset of serum disease is probably, therefore, a visible evidence of the development of general sensitiveness and represents a more or less violent reaction between the circulating antigen and antibody which is in process of development, certainly in the cells, but possibly too in the circulating blood. It is followed by a rapid expulsion of antibodies into the circulation, and shortly afterward by a period of hypersensitiveness, at which time the reinjection of serum may call forth a violent general reaction. Subsequently this period of hypersensitiveness diminishes and antibodies may disappear from the circulation. The injection of serum at this time, owing to the slight concentration of antibodies, does not produce an immediate general effect, but excessive antibody formation under these circumstances, as von Pirquet and von Dungern have shown in the case of precipitins, is much more rapid than in the normal individual and the general reaction, or accelerated serum sickness, appears. Finally, with a complete loss of sensitiveness, the individual returns to the normal state and the reaction is of the normal type.

There is not time to discuss the question as to whether the union of antibody and antigen is of chemical nature, whether it depends upon fermentation, or whether, as is the view that Zinsser[48] has brought forward, some change in the physical properties of the serum determines the union of these two substances. To elucidate the actual nature of the toxic substance that is formed by this union, much thought and experimentation have been expended. It is only a step from the early observations of Pfeiffer,[49] and Wolff-Eisner[50] upon the poisonous products of bacterial disintegration to the work of de Waele,[51] Biedl and Kraus,[52] Vaughan,[53] Friedberger,[54] Weichardt and Schittenhelm,[55] and many others who have shown that the products and by-products of protein digestion when injected into various animals may cause symptoms almost identical with true anaphylactic shock. These observations soon suggested that with the union of antibody and antigen the antigen or foreign protein is digested to form poisonous split products. To confirm this idea evidence has been brought forward by Abderhalden,[56] Cammerer and Pincussohn,[57] by Pfeiffer and Jarish,[58] G. Zung and György[59] and by Jobling and Petersen,[60] to show that during anaphylactic shock in dogs products of protein digestion appear and that the non-protein nitrogen, together with the proteose of the serum, are distinctly increased.

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[44] Tr. Cong. Am. Phys. and Surg., 1910, viii, 402.

[45] Jour. Pharmacol. and Exp. Therap., 1910, i, 549. Bull. 80, Hyg. Lab. U. S. P. H. and M. H. S., 1912.

[46] Jour. Pharmacol. and Exp. Therap., 1913, iv, 167.

[47] Jour. Med. Research, 1914, xxx, 87, 299.

[48] Arch. Int. Med., 1915, xvi, 223.

So far we have discussed only artificial sensitization in man, but it is now necessary to direct attention to a state in which sensitiveness to foreign proteins exists without the known introduction of these proteins. It has been repeatedly observed that the first injection of any foreign serum may be attended in man by a violent immediate reaction. One of the earliest instances to come into prominent notice was the immediate death of Prof. Langerhans's young son after receiving for the first time an injection of diphtheria antitoxin. Gottstein[61] reported a few such cases in 1896, and in 1909 Gillette[62] collected from the literature 30 in which sudden collapse or death followed immediately upon the first injection of antitoxin. It is important to note that 22 of these cases gave a history of asthma or of some respiratory disease. The patient immediately after the injection shows great uneasiness; perhaps complains of constriction in the chest; has violent dyspnea; the face swells and becomes purple; he falls in collapse and may be dead in five to ten minutes. In attacks which are somewhat less fulminant there is violent asthma, cyanosis, collapse, and a giant urticarial eruption. These perhaps are the most striking and certainly terrific demonstrations of spontaneous sensitiveness to foreign protein, but they only repre-

[49] Ztschr. f. Hyg. u. Infektionkrankh., 1892, xi, 293.
[50] Centralbl. f. Bakt., 1904, xxxvii, 390, 566, 684.
[51] Bull. Acad. Roy. de Méd. de Belgique, Brux., 1909.
[52] Wien. klin. Wchnschr., 1909, xxii, 363.
[53] Loc. cit.
[54] Ztschr. f. Immunitätsf., orig., 1911, ix, 369.
[55] Ztschr. f. exp. Path. u. Therap., 1912, x, 412, 448; xi, 69.
[56] Ztschr. f. physiol. Chem., 1912, lxxxii, 109.
[57] Ibid., 1909, lix, 293.
[58] Ztschr. f. Immunitätsf., orig., 1912-13, xvi, 38.
[59] Ibid., 1915, xxiii, 402.
[60] Jour. Exp. Med., 1915, xxii, 401.
[61] Therap. Monatsh., 1896, x, 269.
[62] New York State Med. Jour., 1909, ix, 373.

sent one of the many such sensitizations which have been long recognized as idiosyncrasies. The early work in 1873 of Blackley[63] upon hay fever I have already mentioned. It is of considerable historical interest to note that he associated this condition as early as 1853 with the inhalation of pollen grains, and showed definitely that the instillation of certain pollens in the nose and eye produced in hay fever patients edema and congestion of the mucous membrane with lacrimation. He also made the important observation that pollen grains rubbed into a scarification of the skin called forth an intense itching and local edema. The work of Dunbar,[64] in 1903 and 1904, showed that this was a specific reaction, and later Weichardt[65] brought out the fact that it was due to the protein of the pollen. From this it was only a step for Wolff-Eisner,[66] in 1906, to suggest that hay fever had its origin in sensitization to proteins of various pollens, and later to apply this principle to the explanation of the origin of the urticarias succeeding the ingestion of certain foods.[67]

So common, indeed, is this conception of protein sensitization that attempts have been made to explain thereby all physiological and pathological processes from childbirth to epilepsy. But in spite of these unwarrantable views it is certainly an important factor in some pathological processes, and for this reason it is highly essential that we should understand accurately what true protein sensitization means and analyze the hypotheses that may be evolved from this fascinating but very obscure subject.

A survey of the literature brings forth many interesting examples of what seem to be true spontaneous susceptibility to various foreign proteins. The symptoms produced from contact with these proteins are usually referred to the respiratory tract, the gastrointestinal tract, and the skin. Hay fever is the example of protein sensitization most thoroughly studied in which the symptoms brought on by contact with foreign proteins are usually confined to the respiratory tract and the conjunctivæ. In a certain proportion of cases of asthma the attack simulates, as the fundamental experiments of Auer and Lewis[68] suggested to Meltzer,[69] mild anaphylactic shock in the guinea-pig, and as has been demonstrated since, it may be precipitated by inhalation, subcutaneous injection, or ingestion of foreign proteins to which the individual is sensitized. The most striking examples are to be found in the patients whose attacks invariably occur when they come in close contact or even in the near vicinity of such animals as horses, dogs, cats, rabbits, or mice; or

[63] Experimental Researches on the Cause and Nature of Hay Fever, London, 1873.
[64] Deutsch. med. Wchnschr., 1903, xxix, 149.
[65] Centralbl. f. Bakt., 1906, xxxviii, 493.
[66] Dermat. Centralbl., 1907, x, 164.
[67] Wolff-Eisner, Das Heufieuer, München, 1906.
[68] Jour. Exp. Med., 1910, xii, 15.
[69] Tr. Assn. Am. Phys., 1910, xxv, 66.

in patients who develop from their hay fever true paroxysms of asthma. The subcutaneous injection of even the minutest quantities of solutions of these proteins will precipitate violent paroxysms of asthma, and it is in such spontaneously sensitized individuals that the first injection of diphtheria antitoxin has produced violent symptoms or death.

The gastro-intestinal disturbances dependent upon sensitization to eggs, which is not uncommon in children, and may occur in adults, has been studied, especially by Schloss,[70] Lesné and Richet fils[71] and Talbot.[72] Sensitization to cow's milk, as recently pointed out by Kleinschmidt[73] is another cause of gastro-intestinal disturbances in children. H. L. Smith[74] first drew attention to the importance of sensitization in a case of buckwheat poisoning and similar symptoms after eating such foods as strawberries, melons, or other fruits or vegetables, certain form of meats and shellfish, are widely recognized and are familiar as idiosyncrasies.

Various skin eruptions are associated with direct or indirect contact with foreign protein. In some instances an urticarial eruption always follows contact with the fur of one or another animal or the juice of plants. Wechselmann[75] has described a form of dermatitis which comes on in satinwood workers ten to fourteen days after they start their work. Talbot and Lesne and Richet have especially called attention to eczema which so frequently is seen in children sensitive to egg-white and milk. An increased susceptibility which Goldschmidt[76] has described, to the irritating odor and juices coming from the living ascaris, is probably to be classed with these cases.

A few instances of hypersensitiveness to the sting of insects are described. I know of one individual in whom the sting of the mosquito produces enormous areas of edema similar to the so-called angioneurotic form, and in another case a sting of a wasp was followed by symptoms exactly like the immediate reaction in serum disease. Great local swelling with erythema and edema, collapse, general urticaria; joint pains appeared immediately on two occasions after this individual was stung. Finally, there is a very definite group of cases, of which I have seen several, in whom suddenly, without assignable cause, the patient is stricken with an illness which is precisely like serum disease, and which may recur at the end of several months. At the onset there may or may not be nausea and vomiting, but always there is a general urticaria associated with slight fever, swollen tender lymph nodes, arthralgia, and usually a mild albuminuria. Indeed, some of the attacks of Hennock's purpura are not unlike serum disease, and we have found at least one case sensitive to several foreign proteins. Even more obscure pathological processes, such as eclampsia, have been explained upon the basis of protein sensitization, in this instance, to the chorion or fetal tissues; but the evidence for such assumptions at the present time does not admit of further discussion of these very obscure conditions.

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[70] Am. Jour. Dis. Child., 1912, iii, 341.
[71] Arch. d. mal. d. infants, 1913, xvi, 81.
[72] Boston Med. and Surg. Jour., 1914, clxxi, 708.
[73] Monatsh. f. Kinderh., 1913, xi, 644, orig.
[74] Arch. Int. Med., 1909, iii, 350.
[75] Deutsch. med. Wchnschr., 1909, xxxv, 1389.
[76] München. med. Wchnschr., 1910, lvii, 1991.

Reference must be made here to the interesting drug susceptibilities which apparently may be spontaneous or acquired after the repeated subcutaneous or intravenous use of certain chemicals. In this connection reactions to the iodin and arsenic compounds have been most carefully studied. Stäubli[77] and Kaufman[78] have called attention to the increasing local inflammation which patients are likely to experience after repeated injection of cacodylate salts. With the introduction of salvarsan many observers have noticed anaphylactic-like symptoms during the intravenous administration of this drug. Iwaschenzoff[79] has reported many such instances, and Draper,[80] who has observed it in about 55 per cent. of all treated cases, states that it is never noted at the first injection, rarely at the second, and that if it occurs at all it usually does so at or after the fourth. The patient complains of oppression in the chest, is restless, has dyspnea, shows suffused face and conjunctivæ, and cyanosis. Afterward there may be vomiting and occasionally a blotchy urticaria appears.

Up to the present time it is not known that antibodies are produced by any substances other than those which contain a high protein molecule, and at first the explanation of these reactions was difficult. Friedberger and Ito[81] have called attention to the fact, however, that the serum of a guinea-pig may be so altered by treatment with the tincture of iodin that a mixture of the two will sensitize the guinea-pig to subsequent injections of the same mixture of its own serum and iodin or sodium iodin or to Logul's solution. A first injection of Lugol's solution sensitizes to this mixture of serum and iodin but not to potassium iodin or to Lugol's solution alone. Swift[82] has been able to obtain essentially the same results with salvarsan, and the explanation given by these observers for the iodiosyncrasies to iodides and the anaphylactic-like symptoms after the intravenous injection of salvarsan is that the combination of the drug with the patient's serum forms a new protein compound to which he may be actively sensitive. The reports by Bruck[83] and Klaussner[84] of passive sensitization with the serum of patients showing drug idiosyncrasies have been disproved by Zieler[85] and Pöhlmann.[86]

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[77] Deutsch. med. Wchnschr., 1912, xxxviii, 2452. [78] Ibid., 1913, xxxix, 272.

[79] München. med. Wchnschr., 1912, lix, 806.

[80] Jour. Am. Med. Assn., 1916, lxvi, 400.

[81] Ztschr. f. Immunitätsf., orig., 1912, xii, 241.

[82] Jour. Am. Med. Assn., 1912, lix, 1236.

[83] Berl. klin. Wchnschr., 1910, xlvii, 517, 1928.

[84] München. med. Wchnschr., 1910, lvii, 1451; 1983. 1911, lviii, 138.

These examples, and they might be multiplied many times, represent a group of morbid conditions which have received most study up to the present time. A careful comparison of the symptoms following an injection of foreign protein in the sensitized man with those seen in various animals during anaphylactic shock shows a close similarity. The multiplicity of symptoms is greater in man than in any other one animal. But even typical serum disease has been observed in calves by Beclere, Chambon, and Menard,[87] and in rabbits we have noticed enlargement of the lymph nodes with subcutaneous edema from the sixth to the tenth day after intravenous injection of large quantities of horse serum.

Besides this similarity between the symptoms in man and animals there is a close analogy between the development of specific immune bodies in the two species. This was especially emphasized in considering serum disease, and the same type of immune bodies has been shown to exist in the spontaneously sensitized individual.

Precipitins to cow's milk have been found in the serum of nurslings by Kleinschmidt, and Clowes[88] and Koessler[89] have noted precipitins for pollen in the serum of hay fever patients. Bruck[90] was able to sensitize guinea-pigs passively to pig serum with the blood of a patient who developed violent gastro-intestinal spasm and urticaria after eating pork. Similar results were obtained by Schloss[91] with the serum of his patient, who was sensitive to egg-white, and by Koessler with the serum from cases of hay fever.

The specific skin sensitiveness which is obtained in immune rabbits and guinea-pigs, and which is a characteristic of the artificial sensitization by antitoxic sera in the human being, is an especially prominent feature of the spontaneously sensitized.

The application of minute quantities of specific protein to the skin of such a patient causes a severe local urticaria and erythema, and just as the skin reaction has been employed to estimate the degree and persistence of sensitization in people subjected to one or two injections of antitoxic sera, so it has been used now quite extensively by Schloss, Talbot, Koessler, Cooke,[92] Goodale[93] and others to determine the protein to which these people may be sensitive. There can be no doubt that the skin sensitiveness is solely dependent upon the introduction of protein, for Schloss obtained cutaneous reactions in his case of egg idiosyncrasy with pure ovamucin, ovoglobulin, ovoalbumin, and ovomucoid. We, too, have obtained striking skin reactions with chemically pure phaseolin, prepared from beans and kindly sent us by Profs. Mendel and Osborne, of Yale.

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[85] München. med. Wchnschr., 1912, lix, 401; 1641.

[86] Ibid., 1914, lxi, 543.

[87] Ann. d. l'Inst. Pasteur: 1896, x, 567.

[88] Proc. Soc. Exp. Biol. and Med., 1913, x, 69.

[89] Forchheimer's Therapeutsis, 1914, v, 671.

[90] Arch. f. Dermat., 1909, xcvi, 241.

[91] Loc cit.

[92] Laryngoscope, February, 1915.

[93] Boston Med. and Surg. Jour., 1914, clxx, 837.

An analysis of the conditions of sensitiveness in these patients, however, shows that they differ in some respects from the artificially sensitized. In the first place the degree of hypersusceptibility is generally much greater than is ever reported in the artificially sensitized. In the second place the sensitization is usually multiple, and in the third place the method of sensitization is problematical.

Not only is the increased susceptibility seen in the general violent reactions following subcutaneous and intravenous injections of the specific proteins which may be so great that a subcutaneous injection of 1 c.c. of 1 to 1000 dilution of serum, or as stated by Koessler, 1 c.c. of a 1 to 50,000,000 dilution of pollen extract will bring about general urticaria and asthma, but it is also noticeable in the response of the skin and mucous surfaces. Patients artificially sensitized with horse serum rarely develop horse asthma, though such a thing is possible, for Sewall[94] reports an attack of rabbit asthma in a man who has been injected with rabbit serum. Mere contact with horses will not produce anaphylactic symptoms in guinea-pigs sensitized to horse serum, though instillation of serum into the nose or trachea will do so. Even rarer are gastro-intestinal symptoms following ingestion of proteins to which either man or animal has been actively and artificially sensitized. In the sensitized guinea-pig numerous observers have attempted to produce shock by way of the gastro-intestinal tract, but all have met with complete failures. We have seen, on the other hand, that gastro-intestinal symptoms are common in the individual with spontaneous sensitization. The relative susceptibility of the skin and mucous membranes in these individuals may, however, vary greatly, and though the inhalation or intradermic injection of foreign protein may bring about general urticaria and asthma, ingestion of the same protein may be absolutely harmless and without the slightest effect upon the gastro-intestinal mucosa. Thus one of our asthmatics whose skin was highly sensitive to sheep serum and who on several occasions develped urticaria and asthma after a minute subcutaneous injection, could take by mouth large quantities of sheep serum without the slightest gastro-intestinal symptoms.

The second point of difference, namely, the multiple sensitiveness, is very difficult to interpret. Whereas the artificial sensitization of both man and animals is within limits specific, these patients frequently give a history not only of idiosyncrasies to more than one substance, but as most observers who have studied their skin reactions have noted, give positive skin tests to several different proteins. In the patients whom Dr. Rackamann and I have investigated, this has been quite regularly noted. We have found, however, that the skin reaction and occasionally the general reaction is limited to certain groups of proteins. Patients can thus be roughly classified as those who react to the sera of animals, those who react to eggs or the sera of fowls, those who react to the extract of shellfish, and those that react to the protein of plants. Occasionally the same individual may show sensitization to two or three groups, but, as a rule, it is confined to one. These reactions, too, we have found are not limited solely to abnormal patients, since in a long series of apparently healthy individuals we have found two or three who show skin sensitiveness to two or more foreign proteins.

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[94] Arch. Int. Med., 1914, viii, 856.

It is, of course, possible, as was shown early by Rosenau and Anderson, to sensitize the guinea-pig to at least three different proteins, to each one of which the animal will react specifically, and one might suppose the same could easily happen to human beings once the path to sensitization was open. Besides this it is known, that only within certain limits is the anaphylactic reaction specific inasmuch as guinea-pigs highly immune to the serum of one animal will show mild anaphylactic symptoms when injected with the serum of a closely allied species. This is especially true for man and ape, horse and ass, while Wells and Osborne[95] have shown that the same is true of plant proteins, for an interanaphylactic reaction takes place between chemically pure gliadin from wheat and hordein from barley.

The wide range of sensitiveness, however, and the great unlikelihood that the person might come in contact with many of these proteins, makes it very doubtful whether this, which is accepted by some as an explanation, is correct.

A second possibility, namely, that the sensitization is non-specific, must be considered. It is known that when native proteins are heated or brought into contact with alkalies or other chemical agents their physical properties are injured and they no longer give specific biological reactions. References has already been made to the effect that iodin and salvarsan may have. The protein under these circumstances is said to be denatured. By this process of denaturizing, Landsteiner and Prasek[96] were able to destroy partially the specific precipitin reaction to horse serum. It is possible to conceive, therefore, that during a natural process of sensitization, through whatever route, the native protein is denatured, and when it comes in contact with the cells and tissue juices, produces a non-specific sensitization. This might be especially true if the protein enters the body by way of the gastro-intestinal tract, and is accepted as the explanation by Otto and Hoefer.[97]

Although the mode of sensitization might seem at first glance easy to explain, there are certain factors involved that really make its

[95] Jour. Inf. Dis., 1913, xii, 341.

[96] Ztschr. f. Immunitätsf., orig., 1914, xx, 211.

[97] Ztschr. f. Hyg. u. Infektionskrankh., 1915, lxxx, 1.

interpretation very difficult. The paths open for such a sensitization are, of course, numerous. Wounds of the skin and mucous membranes might readily be held responsible, and even through the unbroken mucous membrane sensitization may be accomplished in animals. The history of many of these cases of spontaneous sensitization suggests that the process has taken place by one of these routes. But such an explanation is not applicable to all cases, and cannot account for the fact that an infant shows violent symptoms the first time it is fed an egg.

The history of idiosyncrasies in certain families, such as the tendency to asthma or hay fever, or the susceptibility to certain foods, has long been recognized as very common. Cooke obtained a history of some idiosyncrasies in the immediate families of 129, or 63.8 per cent., of 205 cases of hay fever, and everyone who has written on the subject of asthma draws attention to the familial tendency, Lesné and Richet report the occurrence of egg sensitiveness through three generations. Inheritance must, therefore, be considered as a possibility. Immunity to certain poisons may be transmitted from mother to offspring, and it has been definitely shown by Rosenau and Anderson,[98] Gay and Southard,[99] and by Lewis[100] that the same is true of hypersensitiveness to horse serum in guinea-pigs. Hypothetically this may take place in one of three different ways: as true inheritance through the germ plasm of the cells, either of the father or mother; second, by direct influence of the immunizing agent that affects the mother, upon the cells of the fetus, which would produce active immunity in the child. Third, by passive transference of the immune bodies from mother to fetus by way of the blood or milk.

It was shown by Ehrlich[101] in studying the transmission of abrin and ricin immunity in mice that this is conferred only by the mother, and that even when the mother is immunized during pregnancy the immunity in the offspring lasts but a few weeks. He concluded that this was, therefore, in no sense of the word a true inheritance, but the passive transference to the fetus or child of immunity through the blood or milk of the mother. The immunity is not transmitted to the second generation. The same principle has been established in the transference of other forms of immunity and in experimental anaphylaxis. Groer and Kassowitz[102] have concluded from a recent study that the antitoxin for diphtheria, which Schick showed was present in the blood and tissues of many human beings was transmitted passively from mother to infant through the placenta. The facts so far collected regarding the familial tendency of idiosyncrasy to foreign protein

[98] Loc. cit.

[99] Loc. cit.

[100] Jour. Exp. Med., 1908, x, 1; 608.

[101] Ztschr. f. Hyg. u. Infectionskrankh., 1892, xii, 183.

[102] Ztschr. f. Immunitätsf., orig., 1914, xxiii, 108.

do not accord absolutely with those observed in experimental transference of immunity and anaphylaxis from mother to offspring. In the first place, sensitization in man is not transient but often of years' duration. In the second place it may occur through four generations, and in the third place it is often noticeable principally or solely, as occurred in the extraordinary family described by Laroche, Richet and St. Girons,[103] in the male members. And finally, the sensitization may not always be to the same protein. In at least one family which we studied the father was sensitive to horse serum and the son to egg-white. If inheritance is a factor, therefore, it cannot be by means of passive transfer from mother to infant, but in some instances, at least, may be a true inheritance of cell characteristics derived either from the father or mother. The whole problem, since it is one of greatest importance, needs careful study, but one is almost inclined to suggest that occasionally sensitization toward foreign protein may be an inherited characteristic of the cell plasm and often not highly specific in character. Whether this is dependent upon the presence of true antibodies to the foreign protein or ferments, as Abderhalden and others have suggested, it is impossible to say. That receptors in the sense of Ehrlich for sheep cells may reside in the organs of such species as lobsters, crabs, chickens, and dogs, has been shown by Amako,[104] and more important still is the demonstration of von Dungern and Hirschfeld[105] that the isoagglutinins are inherited and transmitted strictly according to Mendelian law.[106]

The high degree of susceptibility in some people with spontaneous sensitiveness, the multiplicity or lack of specificity of sensitization, and the distinct tendency for it to occur in families differentiate these individuals from the artificially sensitized, and suggest that there is some unknown factor here which is absent in men and animals subjected to artificial sensitization.

The introduction of foreign protein, however, results in essentially the same reaction in both instances and individuals in this state of spontaneous sensitization suffering from the effects of contact with protein ordinarily harmless must clearly be differentiated from the normal person who becomes ill from the absorption of one of the poisonous products which may through various means be split off from the protein molecule.

Undoubtedly certain violent intoxications in man are caused by the entrance into the body of these toxic products of protein digestion, and it is possible that they may give rise to symptoms which resemble the true anaphylactic shock. The rupture into the peritoneum of an echinococcus cyst is frequently attended by violent symptoms of collapse which Weinberg and Ciuca[107] have ascribed to anaphylactic shock. But as it is difficult to sensitize animals to the fluid of echinococcus cysts, or to show that animals or men carrying echinococcus cysts are sensitized to the fluid, and since the fluid itself is toxic, Graetz[108] concludes that the symptoms after rupture are not due to anaphylaxis but to the absorption from the peritoneum of toxic products split from the protein of the cyst.

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[103] Gaz. d. hôp., 1912, lxxxv, 1969.

[104] Ztschr. f. Immunitätsf., orig., 1914, xxii, 641.

[105] Ibid., 1909–10, iv, 531.

[106] Since this lecture was delivered the important work of Cooke (Jour. Immun., 1916, i, 201) has been published. He has shown from a clinical study of the family history of a large group of patients suffering from such evidences of protein sensitization as hay fever and susceptibilities to certain foods, that sensitization affects members of families in a proportion which closely approximates the theoretical figures of the Mendelian law and suggests that sensitization is inherited in the strict sense and is transmitted as a dominant characteristic.

The investigations of Whipple[109] and of Murphy and Brooks[110] upon the acute poisoning in dogs whose duodenum has been closed off in a loop, have shown that the symptoms are due to a toxin absorbed through the duodenal mucosa, and recently Whipple, Rodenbaugh, and Kilgore[111] have been able to isolate this toxin and show, as they believe, that it is proteose. It may be, therefore, that the acute collapse and toxic symptoms that accompany some of the severe gastro-intestinal disturbances are caused by the absorption of proteoses or such substances as histamin. These poisonous substances may be taken into the gastro-intestinal tract with the food, especially if it is spoiled, or they may be present there already. Such attacks of food poisoning are perfectly familiar, but it is questionable whether they result in sensitization, and they should not be confused with anaphylaxis.

So far our attention has been concentrated wholly upon the susceptibility of man to the proteins of animals and the higher plants or their split products, but it is necessary now to refer, at least briefly, to a somewhat different form of susceptibility but one of great importance, namely, "allergy" or changed reactivity or hypersusceptibility to infection.

The principle is beautifully illustrated by the classical experiments of von Pirquet on vaccination. Cutaneous inoculation of the normal individual by the virus of vaccinia results in the appearance after an interval of nine to twelve days of the typical skin lesion or local vaccinia, the normal reaction. Vaccination of a person recently immunized to cowpox shows within twenty-four hours the appearance of a small vesicle surrounded by a red areole which rapidly fades, and revaccination after several years results in a positive "take" which, however, appears early on the sixth or seventh day instead of the ninth or twelfth day as it does in the normal individual.

[107] Compt. rend. Soc. de biol., 1913, lxxiv, 1318; 1914, lxxvi, 340.
[108] Zeit. f. Immunitätsf., orig., 1912, xv, 60.
[109] Jour. Exp. Med., 1913, xvii, 286, 307; 1914, xix, 166.
[110] Arch. Int. Med., 1915, xv, 392.
[111] Jour. Exp. Med., 1916, xxiii, 123.

The similarity to the normal immediate and the accelerated reactions on inoculation and reinoculation of horse serum is very striking, and was immediately apparent to von Pirquet.

The relationship which anaphylaxis bears to this broad field of immunity and susceptibility, and the part which the poisonous products of protein digestion may have in causing the symptoms of infections, such as fever, was thoroughly discussed by Dr. Vaughan two years ago, and I shall therefore confine myself to one phase of the subject which will still repay study.

A method of studying the allergy to infection in man which has been developed within the last few years is the altered local reaction to the conjunctival, subcutaneous, or intracutaneous injection of bacteria or their extracts. The reaction of the conjunctiva and the skin of tuberculous patients to tuberculin is perfectly familiar. Similar specific reactions have been obtained with the extracts of bodies of the infecting bacteria in such disease as glanders, typhoid fever, syphilis, the trichophytic infections, and lobar pneumonia. In general it may be said that the response to the injection of these organisms or their extracts appears either during the course of the infection or after recovery of the individual. The tuberculin reaction, according to most observers, appears in animals fifteen to twenty days after infection by the tubercle bacillus. The typhoidin reaction of Gay can be obtained many years after recovery from typhoid fever. Müller, Gachtgens, and Aoki[112] who have studied the development of the mallein reaction in glanders in horses, state that the skin test may give a positive result on the fourth or fifth day after infection, and Weil,[113] who has recently described a cutaneous reaction obtained in a certain proportion of cases of pneumonia, when the autolysates of pneumococci are employed, states that the reaction first appears after the crisis.

The pathology of all these reactions is very similar, and though the histology of the lesion has only been studied extensively in tuberculosis, the few observations which have been made of the other reactions indicate that they resemble one another very closely, and consist principally in the infiltration of the subcutaneous tissues by mononuclear cells which are collected about bloodvessels. Unlike the reactions obtained with animal and vegetable proteins in sensitized individuals these reactions do not come on within the first few hours after inoculation, but make their appearance first in twenty to forty-eight hours. The tuberculin reaction may be delayed for two or three days and the luetin reaction for ten days to three weeks.

It is possible that similar local forms of allergy occur spontaneously during the course of many diseases. In the cases of chronic infections by the Streptococcus viridans the cutaneous hemorrhages and painful nodules have been supposed to result from emboli to the skin, but Dr. Lamb, in studying a few of these lesions in serial section, has been unable to find thrombosed vessels. The histological picture is again not unlike that seen in the tuberculin reaction. Quite similar is the change in the glomeruli of the kidney so common in these cases and so unlike the acute suppurative processes usually encountered in acute infections, that it is possible it may represent an allergic reaction toward the infecting organism.

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[112] Ztschr. f. Immunitätsf., orig., 1910, viii, 326.
[113] Jour. Exp. Med., 1916, xxiii, 11.

Faber[114] has recently shown that a previous injection of streptococci into the joint of a rabbit will alter the local resistance of the joint in such a way that intravenous injections of that type of streptococci which in normal animals rarely, if ever, affects the joints, invariably produces in the treated animals a localized infection of the joints in these animals. This local allergy seems, too, to be specific. Finally, one may cite the transition of an acute local infection to a chronic local inflammation as a beautiful example of allergy or changed reactivity to an infecting organism. It is worthy of notice, too, that many of these local allergic processes are associated in human beings with the appearance of mononuclear cells. In rabbits the polymorphonuclear leukocytes predominate both in the tuberculin reaction and in that obtained with animal proteins.

During the artificial immunization of both man and animal by repeated subcutaneous injections of bacteria or their extracts both local and general reactions occur which must be interpreted as an evidence of allergy. It is generally recognized that severe local and general reactions are much more likely to occur in patients who have had typhoid fever or who have been subjected to previous inoculation than in normal individuals, and that the local or general reaction in normal persons is more likely to be severe following the second or third inoculation than after the first. Nichols[115] states that severe local reaction occurs in 50 per cent. of cases after repeated inoculation. In very rare instances the general reactions following large injections of bacterial vaccines spaced at long intervals are immediately followed by alarming collapse, swelling of the face, dyspnea, and suppression of urine a condition not unlike anaphylactic shock.

Indeed many of these condition have been ascribed to sensitization, likened to anaphylaxis and accepted as such. Bacterial bodies contain nucleoproteins, the proportion of nitrogen varying in different bacteria from 8 to 10 per cent., and it cannot be doubted that it is possible to produce anaphylaxis with bacteria or their products though the primary toxicity of these suspensions and extracts is often so great that the results of many experimenters leaves one in doubt as to whether the effect of injection is really that of anaphylactic shock or some other form of rapid intoxication. In working with bacteria the results are always complicated by the presence of poisonous substances, whatever their origin, and until it is possible to obtain from bacterial bodies proteins free from the toxic split products, or substances developed from bacterial growth, it will be difficult to determine what part the true protein sensitization and the anaphylactic reaction plays in susceptibility and infection.

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[114] Jour. Exp. Med., 1915, xxii, 615.

[115] Ibid., 780.

Even the extensive studies upon tuberculosis have not completely explained the reactions which Koch's O. T. tuberculin, which is a glycerin broth filtrate, calls forth. In general the reactions produced in the tuberculous individual differ very slightly from those obtained with bacillus emulsion or extracts rich in protein, but with the latter animals may be readily sensitized, while with the former, though such sensitization has been accomplished, it is with great difficulty, and the reactions according to Lewis[116] are dependent upon the protein in the broth rather than in the extract from the bacilli. Though Baldwin[117] showed that animals may be sensitized with tuberculoprotein as with other bacterial proteins, most workers have failed to sensitize guinea-pigs passively with the serum of tuberculous patients or animals. Austrian[118] has shown that such a thing is possible if tuberculoprotein instead of Koch's O. T. tuberculin is used as antigen. Animals actively sensitized to tuberculoprotein may give a very faint skin reaction to O. T. tuberculin, though the infected animals, of course, react strongly. In fine, the skin reaction and the general reaction to O. T. tuberculin seem to depend upon the presence in the body of an active tuberculous focus, and Bail[119] in transplanting tuberculous tissue from a tuberculous to a normal animal found that the reaction after the injection of tuberculin always takes place in the tuberculous tissue. It is evident, therefore, that though the reaction in the tuberculous patient or animal is the same whether tuberculoprotein or O. T. tuberculin is employed, the anaphylactic reactions differ greatly and cannot be obtained with the latter.

To what extent the forms of allergy, such as the diagnostic skin reaction, in other infectious processes are dependent upon protein sensitization, and can thus be accredited to true anaphylaxis, is uncertain, but before sweeping conclusions can be made upon the identity of allergy and anaphylaxis much careful experimental work is necessary.

The analogy is very close, however, and since one of the striking features in infectious processes is the response on the part of the body by exudation and proliferation of cells, namely, an inflammation, it is important to determine whether similar processes accompany or follow anaphylactic reaction to simple proteins. The characteristic result of acute shock in guinea-pigs is the appearance of hemorrhages. But the guinea-pig that has recovered from a single shock shows no permanent trace of these lesions. Repeated injections of serum made subcutaneously in rabbits, on the other hand, give rise to edema, hemorrhage, and necrosis, as was pointed out by Arthus, and the lesion is characterized according to Schlecht and Schwenke[120] by an exudation of mononuclear cells and eosinophilic leukocytes. Friedberger and Mita[121] and Ishioka[122] showed, too, that horse serum sprayed into the trachea of sensitized guinea-pigs produced a cellular type of pneumonia, the exudate into the alveoli being rich in mononuclear cells and eosinophiles. We[123] have found that repeated intravenous injections of horse serum and egg-white in sensitized guinea-pigs, rabbits, dogs, and cats brought about focal necroses in the liver, kidney, and heart muscle which was followed by an exudation of mononuclear cells. In over 80 per cent. of the animals changes were found in the kidneys which were often so extensive that they led to an advanced form of nephritis.

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[116] Arch. Int. Med., 1909, iv, 528.
[117] Jour. Med. Research, 1910, xxiii, 189.
[118] Jour. Exp. Med., 1912, xx, 149. Bull. Johns Hopkins Hospital, 1913, xxiv, 280.
[119] Ztschr. f. Immunitätsf., orig., 1911-12, xii, 451.

Though it would not be justifiable to apply the results of such experiments to disease in man, it is interesting to note that one of our patients who showed spontaneous sensitiveness to several proteins from plants, and especially to phaseolin, and who had had several violent attacks of asthma, urticaria, and diarrhea after eating beans, developed a pronounced and persistent albuminuria and cylindruria following such an attack one year ago. Undoubtedly infection is the most important factor in the cause of nephritis in men, but such observations suggest that the progressive process in the kidney may depend upon an allergy or altered susceptibility of this tissue towards the bacterial proteins.

It is known that about 10 per cent. of patients with serum sickness have a mild degree of albuminuria and show both hyaline and granular casts in the urine, and it was, therefore, with much interest that Dr. Rackemann and I studied the functional activity of the kidney during the course of this disease. Most of the patients have developed their serum sickness after the use of large amounts of antipneumococcus serum, which Dr. Cole has kindly furnished us for the treatment of pneumonia caused by the pneumococcus type I. In this study attention has been paid especially to the excretion of phenolsulphonephthalein, water, and sodium chloride. The nitrogen metabolism is so much disturbed during and after an attack of pneumonia that little significance can be attached to the changes in the total non-protein nitrogen of the blood. The coefficient of urea excretion, however, employed by Ambard has been studied by the recent modification in technic described by McLean,[124] and we have not found that this is greatly modified during serum sickness. The excretion of chlorides and water, on the other hand, is often profoundly affected. The changes that take place in the elimination of salt and water during convalescence from an attack of pneumonia, that has not had serum are as follows: During the attack the excretion of water is low and the chlorides are eliminated in small amounts and low concentration. Shortly after the attack the retained chlorides are excreted in excess of the intake and in high concentrations, but on a fixed water and salt intake soon come to a normal balance. We have not found that this course is materially interfered with by such febrile complications as empyema. In the serum sickness that may follow the use of antipneumococcus serum, and in one case after the intraspinous injection of antimeningococcus serum, the ordinary course of the elimination of water and sodium chloride is greatly disturbed. With the onset of serum disease the excretion of water diminishes rapidly and with it the elimination of sodium chloride. One important point, too, is that the patient is unable to concentrate the sodium chloride, which may fall below 0.2 per cent., a very low figure. The excretion of phthalein is in a few cases slightly affected as well, and with the appearance of albumin and casts in the urine and the development of edema, the patient present a clinical picture very closely resembling a mild case of nephritis, of the salt retention type. Sufficient studies have not been made to determine whether this salt retention is in the blood or tissues, but at all events it is usually accompanied by edema. These alterations, so far as we have observed them, are purely transitory and with the subsidence of the attack the patient and the renal function return to a normal state.

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[120] Deut. Arch. f. klin. Med., 1912, cviii, 405.

[121] Deutsch. Med. Wchnschr., 1911, xxxvii, 481.

[122] Deutsch. Arch. f. klin. Med., 1912, cvii, 500.

[123] Jour. Exp. Med., 1913, xviii, 678; 1915, xxii, 793. Arch. Int. med., 1915, xv, 1079.

Such studies are designed primarily to throw some light upon the possible importance of repeated anaphylactic shocks in the spontaneously and highly sensitized individual, and it would be the greatest mistake and misfortune at the present time if they were allowed to have any bearing on the use of antitoxic and antibacterial sera. The concentrated diphtheria antitoxin, such as is employed, now rarely produces serum disease or sensitizes sufficiently highly to make a second dose, particularly if it is given subcutaneously, in the least dangerous, and it is only to the spontaneously sensitive who react to the first injection that harm is likely to come.

To prevent accidents in such unexpected instances, especially if large quantities of serum are given intravenously, a preliminary intracutaneous injection of 0.1 to 0.01 c.c. of serum should be made to determine whether or not the patient is spontaneously sensitive to the serum which is to be employed.

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[124] Jour. Exp. Med., 1915, xxii, 212.

Though it would be interesting to recount the methods which have been employed to desensitize both artificially and spontaneously sensitized individuals, this important problem in therapeutics must be left, since there is no time to do it justice, and in conclusion I shall point out the conditions which such methods must combat.

The injection of foreign proteins in man brings about the same condition of hypersensitiveness toward subsequent injections that it does in animals.

Certain individuals may show spontaneous hypersusceptibility to one of several foreign proteins. That these people differ from the artificially sensitized, in that their susceptibility is very great, is shown toward several different proteins, and has a tendency to occur in families. And, finally, that this state is associated with and directly responsible for some well-defined pathological conditions.

THE SYMPTOMS AND PHYSICAL SIGNS RESULTING FROM WOUNDS OF THE CHEST.[1]

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From August 7 to November 1, 1915, there were admitted 3039 to the hospital to which the writer was attached; of these 1315 were sick and 1724 wounded; of the latter, 107 (6 per cent.) received either a gunshot wound or shell wound of the thorax; 20 cases were evacuated too rapidly to permit of a physical examination of the chest. This leaves 87 cases for purposes of analysis.

Forty-five were the result of gunshot wounds, and of these 41 penetrated the thoracic cavity; the remaining 4 were merely wounds of the parietal wall without obvious penetration of the pleural cavity.

Forty-two were the result of shell wounds of some kind, as high explosive, shrapnel, trench mortar, or hand grenades. Of these, 28 had certainly penetrated the chest wall and 14 had apparently not, though 1 at least had caused a fracture of a rib which had lacerated the pleural cavity.

These cases we shall divide into four groups for purposes of description and consideration.

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[1] I wish to express my appreciation to Col. Birkett, Lt. Cols. Elder and McCrae, Majors Hill and Archibald and the other officers of No. 3, Canadian General Hospital, for the opportunity to see the cases and for permission to publish them.

GROUP I. Fifteen patients presented no abnormality in the lungs or pleuræ at the time of the examination. That is to say, 17.2 per cent. of wounds of the chest revealed no injury to lung or pleura a few days after the receipt of the injury, and that in spite of the fact that of these 6 were penetrating gunshot wounds and 1 penetrating shell wound. The remaining 8 had only affected the parietal wall.

GROUP II. A very interesting group of 6 cases comprised 4 cases of pneumonia and 2 of serous pleurisy with effusion. The 4 pneumonias all resulted from shrapnel, 2 of which were penetrating wounds. Further, what was of special interest in 2 cases, the involvement was on the side opposite to the wound. A third case was a double pneumonia associated with paralysis of the vocal cord from a missile lodging in the upper right chest behind the first rib, and was possibly originally an aspiration pneumonia. The fourth pneumonia patient had only a small shrapnel wound of the thorax, but was buried in a trench for some time and consequently much bruised about the thorax. One of the pleurisy, with effusion, cases had an accompanying pneumonic consolidation of the lung resulting from a non-penetrating gunshot wound of the opposite side. The other case was a simple serous effusion the result of a non-penetrating shell wound of the same side.

GROUP III. This includes one case of mediastinitis, resulting from a rifle bullet lodging in the anterior mediastinum. The only symptoms complained of were pain referred to the right side of the neck over the upper and outer border of the trapezius muscle and slight dysphagia. On inspection there was a marked area of ecchymosis over the manubrium, but, of course, as yet, no fulness of the superficial veins. There was in addition a non-fluctuating elevated tender area beneath the discolored skin from the subcutaneous hemorrhage. There was a definite area of dulness corresponding to the anterior mediastinum, reaching above to the upper margin of the manubrium; below merging with the heart dulness, extending to the right about 1 cm. beyond the sternal border and to the left just to the sternal border. On auscultation over the manubrium and raising the patient's arms above his head there was a well-marked grating friction, a sign described by Perez[2] and reported by the writer[3] in other cases of mediastinitis. A skiagram revealed a sharply pointed bullet slightly more than one inch in length lying apex downward behind the manubrium to the right of the midline one inch from the surface.

GROUP IV. This group comprises the hemothorax cases which for purposes of discussion have been further subdivided into the infected and sterile.

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[2] Brit. Med. Jour., 1896, i, 82.

[3] C. P. Howard, Johns Hopkins Hosp. Bull., 1915, xxvi, 140.

A. *Infected Hemothorax.* Of the 65 cases, 9 were definitely infected (13.8 per cent.). This is a somewhat lower percentage than that given by Col. Sir John Rose Bradford[4] in his series in which 25 per cent. of 328 cases were infected. Hale White[5] found only 10 per cent. of the cases in his base-hospital experience in England with evidence of infection of the fluid.

As to the nature of the wounds, 4 were penetrating gunshot wounds, 4 were penetrating shell wounds, and 1 was a non-penetrating shell wound which had caused a fractured rib, a spicule of which had lacerated the pleura and was to all intents and purposes a penetrating chest wound. The infective organism was one of the gas bacillus group in 1 case, B. tetani 1 case, pneumoccus 1 case, streptococcus 1 case, Streptococcus and Staphylococcus aureus one case, and a large unidentified bacillus (recovered on three separate aspirations) 1 case. In the remaining 3 no cultures were made.

Cough, hemoptysis, pain, and dyspnea were present in about the same proportion as in the next group, under which these symptoms will be discussed in detail.

As one might expect, the temperature range was higher in this group than in the non-infected cases, and not uncommonly ran a more or less continuous curve of 103° to 104° F. This fever curve taken in conjunction with the rapid pulse (120 to 140) and a marked tendency to polypnea (28 to 40) would always suggest the chart of ordinary acute lobar pneumonia.

In 2 cases the infection lay dormant for ten days and eighteen days respectively. In the first of these cases a penetrating shrapnel wound was received on September 25; an exploratory aspiration on October 1 revealed a bloody fluid, smears and cultures from which were negative for organisms; a second aspiration on October 5 revealed a number of organisms of the "gas-bacillus group;" a third aspiration on October 7 showed the same organism, though in smaller numbers. The second case received a penetrating gunshot wound on October 13 and ran a normal temperature, pulse, and temperature curve until October 31, when there was a sudden rise in all three (temperature, 104.4°; pulse, 120; respiration, 28), and an exploratory puncture revealed a large bacillus morphologically resembling one of the gas bacillus group, but which grew aërobically as well as anaërobically, did not produce gas, and was unidentified, but probably belonged to the group of diphtheroids found by others in this war; that it was the cause of the infection of the pleural exudate cannot be doubted, as it was found alone on three separate aspirations.

Physical Signs: The physical signs in this group differed in no way from those of the sterile cases. We never found the two signs

[4] Brit. Jour. Surg., 1915, iii, 247.

[5] Lancet, 1915, ii, 1233.

of anaërobic bacillus infection described by Bradford, namely, a rapid displacement of the heart and a "cracked-pot" percussion note from the rapid development of gas within the pleura.

Only 2 of the cases showed definite signs of pneumothorax, while in a third air and pus could be seen and heard sucking in and out of a large wound in the upper back, though none of the characteristic signs of pneumothorax could be detected, but merely those of an extensive fluid exudate. This case interested me much at the time. West[6] reports 2 cases with large wounds of the chest in which the lung did not collapse, though no adhesions were present, and in which there were no signs of pneumothorax. All of us have noted the absence of signs of pneumothorax after thoracotomy for a recent empyema. On the other hand if the empyema be of long standing and firm adhesions have formed, causing pocketing of air and pus, well-marked signs of pneumothorax may be present, as in a case seen recently in the surgical clinic (University Hospital, No. 2609). While infection should be suspected in every case which is not progressing favorably after the fourth day, it cannot be diagnosed on clinical symptoms and signs alone. An exploratory aspiration and a bacteriological examination (both smears and cultures) should be made in all suspicious cases.

As regards treatment, in 4 of the cases a thoracotomy was done, as a result of which 2 were discharged well, 1 improved, and 1 died. One case which was drained at a casualty clearing station by inserting two rubber drainage tubes between the eighth and ninth ribs in the posterior axillary line, died five days later under our care. One case was merely aspirated and was discharged improved, but whether or not he subsequently required more radical treatment is not known. In 3 cases no surgical procedures were instituted: in 1 case because a coexisting tetanus caused death; in 1 case because the patient was moribund upon admission; the third was evacuated to England at the patient's request in an apparently hopeless condition, owing to the existence of a complete paraplegia of the lower extremities

One striking feature of the cases in which a thoracotomy was performed was, in spite of the promptness of the surgical interference, the slowness of the convalescence owing to the marked tendency in these cases to the formation of adhesions and the consequent pocketing of pus that occurred.

B. *Sterile Hemothorax.* This was by far the largest group, comprising as it did 56 patients. Thirty-one were the result of gunshot wounds, of which all but one had penetrated the chest cavity. In 25 shrapnel, hand grenades, or some form of shell was the cause of the wound, 20 of which had obviously penetrated the thoracic cavity; in the remaining 5 no penetration wound was demonstrable, and the hemorrhage must have resulted from laceration of the intercostal arteries or severe contusion of the lung itself.

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[6] Emerson, Johns Hopkins Hosp. Reports: 1913, xi, 375.

The four chief symptoms were cough, hemoptysis, dyspnea, and pain in the chest.

Cough was a most constant symptom, being present in 41 cases, absent in 9, and not noted in 6. In other words, it was present in 82 per cent. of cases in which a definite note was made. For the most part it was the characteristic short, sharp, dry cough of an ordinary pleurisy. Apart from these cases, in which a definite hemoptysis occurred, sputum was strikingly absent

Hemoptysis was also a very constant symptom, being present in 39 cases, absent in 7, and not noted in 10. In other words, in 85 per cent. of the cases blood was expectorated. This varied from a few mouthfuls immediately after the reception of the wound to a more prolonged and repeated hemoptysis persisting in some cases for days. Of course, in the immediately fatal cases which were not seen by us very extensive external hemorrhage must occur in many cases. While hemoptysis is usually due to penetration of the lung, with laceration of a bloodvessel, Rose Bradford[7] believes it might also be due to an infarction of the lung from bruising when there is no proof that the missile had penetrated the lung substance. A fatal hemoptysis occurred only once in 1000 cases studied by this author.

Dyspnea was a somewhat less frequent symptom, occurring in 21, absent in 10 and not noted in 25. That is to say, it was present in approximately 70 per cent. of the cases. It was rarely marked and usually of short duration; even the cases with a small pneumothorax showed at the most slight respiratory embarrassment.

Pain in the chest was present in 24 cases, absent in 7, and not noted in 25. This means approximately 80 per cent. of the patients with a complete history complained of pain somewhere in the chest, usually at the site of the wound, though not infrequently in the axilla or front of the chest. It was always worse on breathing or on movement of any kind.

Fever of varying degree was noted in 47 patients, and was absent in 9 (*i. e.*, 99° or less). That is, 92 per cent. showed fever. Of these 20 patients had a temperature at one time or another of 102° F. or over, and 3 even of 104°. Another 12 had a rise to a point between 100.2° and 101.8°; and 15 between 99.2° and 99.8°. The presence of fever by no means indicated an infection of the pleura or underlying lung, and was due in these cases either to an infection of the parietes or to absorption of the blood contained in the pleural cavity, the latter being analogous to the so-called protein fever of the experimental laboratory.

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[7] Brit. Med. Jour., 1916, i, 129.

The pulse was accelerated in every one of the 56 cases (100 per cent.). In 10 cases it was markedly (120 or more per minute), in 35 moderately (90 to 119 per minute), and in 11 slightly elevated (80 to 89 per minute). This was no doubt due in part to the parietal infection, but chiefly to the physical exhaustion and shock experienced by the patient, as the pulse rapidly returned to normal after proper rest in bed and suitable nourishment. Hemorrhage itself played but a small role, and that only in a small proportion of cases.

Respirations were about normal in 43 of 54 cases (80 per cent.). They were markedly accelerated (*i. e.*, 32 or more per minute) in 12, moderately (25 to 30 per minute) in 14, and slightly (22 to 24 per minute) in 17 patients. In 13 cases the respiratory rate was normal upon coming under our observation at the base.

The physical signs were as follows: *Inspection* yielded invariably a diminished movement of the affected side; in some cases this was exaggerated by the patient's apprehension of causing pain or producing a hemorrhage. Fulness was not a constant feature except in the very extensive effusions. Two or more weeks after the wound one was not infrequently struck with the subsequent retraction of the thoracic wall more than one sees in civil life, except in cases of empyema or fibroid phthisis. This was due to the marked collapse of the lung, and according to writers in England is entirely recovered from as the lung expands from suitable exercises.

Palpation frequently reveals the characteristic crackling of subcutaneous emphysema for a considerable distance around the wound, being present in 10 of our 56 cases. This phenomenon no doubt is due to escape of air from the underlying lung, and is subsequent to a transient pneumothorax, though in only 2 of these cases were the other physical signs of air in the chest present. Of course, the diminished motion could also be detected. Tactile fremitus was diminished in the great majority of cases (90 per cent.), and in the remainder it was either normal (1 case), increased (1 case), or diminished in front and increased behind (2 cases). Increase of vocal fremitus is readily explainable by the compression of the underlying lung, and in our series, considering the other evidence of compression, was surprisingly rare.

Percussion. The note was usually dull in moderate effusions (30 cases) and of a woodeny flatness in the larger effusions (18 cases); in 8 no remark as to the quantity of the effusion was made. A tympanitic note was present in front or above the line of effusion in 4 uncomplicated cases, and was no doubt the Skodaic hyperresonance present in simple effusions above the level of fluid. In 3 other cases, however, the tympany was associated with other suspicious signs of a pneumothorax. In 8 additional cases the tympany occurred in conjunction with other more definite signs of a pneumothorax.

Rose Bradford called our attention to the frequency of an atonic relaxation of the diaphragm, so that the area of gastric tympany was found to extend unusually high on the left side; this phenomenon he does not believe to be due simply to a wound of the lung, for it only appears with hemothorax.[8] We examined for it in too few cases to express an opinion as to its value.

Auscultation. The breath sounds were, for the most part, suppressed or absent (30 cases), but in 19 other cases (39 per cent.) they were noted as bronchial over the back or above the line of effusion. This again shows the frequency and extent of compression of the lung. In 7 cases no note was made as to the character of the breath sounds. The vocal resonance, as determined by the transmission of the spoken voice sound with the aid of the stethoscope, was increased in 11 cases, diminished in 12, and normal in 1 case. In the remainder no note was made. Here again we find evidence of the frequency of compression of the lung.

The transmission of the whispered voice sounds (pectoriloquy) was only tested for in 5 cases, but was present in 4 of these.

Medium or fine moist rales were noted only seven times in spite of the frequency of compression of the lung. A pleural friction was more frequent, being present in 12 cases, in 3 of which it had the pleuropericardial character.

There were 8 cases of undoubted pneumothorax and 5 suspicious cases, and yet a metallic tinkle was heard in only 6 cases and the coin sound or "bruit d'airain" of Trousseau in 4. The Hippocratic succussion was not tested for, owing to the importance of keeping the patients as quiet as possible.

Cardiac displacement was a very constant sign, being present in 23 cases of 32 (72 per cent.) in which a note was made as to the position of the heart. We were much struck with the degree of displacement even when the effusion was relatively small in amount, and considered it to be further evidence of the probable frequency of the existence of a pneumothorax in the early stages of the thoracic injury. The greater density of the fluid as compared with that of ordinary serous effusions did not satisfactorily explain the greater displacement of the heart in these cases. The heart very slowly returned to its normal site even after the effusion had largely subsided, and in many cases the patient was sent to England with considerable cardiac displacement persisting.

Roentgen-ray Findings. In only 20 cases was a skiagram taken, first, as in the cases with a wound of exit it was unnecessary, and secondly, as we moved our patients as little as possible. In 12 of these cases the missile was located in the thorax, in 1 case it had penetrated the diaphragm, and had come to rest in the abdominal cavity. In the other 7 cases no foreign body could be found. In

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[8] J. Rose Bradford and T. R. Elliott, Brit. Jour. Surg., 1915, iii, 247.

3 cases fluid was still present when a search was made for the foreign body. In one other case a pneumothorax still existed.

Complications. In 2 cases there were undoubted signs of fluid on the two sides of the chest, and in a third there were signs of either a small effusion or a marked displacement of the posterior mediastinum and its contents.

As was noted before there were 8 cases of undoubted *pneumothorax* and 5 in which there was more than a strong suspicion. The majority of these cases were admitted within a day or two of one another after the British offensive of September 25 and 26, 1915, when the wounded were evacuated very rapidly to the base. Further, the signs of air in the chest rapidly disappeared, in several instances in twenty-four hours. The greater incidence in those seen shortly after being wounded and the rapid absorption of the air under observation lead us to believe, with all due respect to the opinion of Sir John Rose Bradford,[9] that a mild form of pneumothorax is a common occurrence and must be present in the majority of cases in which a missile has penetrated the lung. It is of interest to know that Otis[10] noted in the American Civil War not more than 6 cases in which a pneumothorax was a troublesome complication. We must admit with Rose Bradford that over an area of cutaneous emphysema the character of the percussion note may suggest the presence of a pneumothorax when none is present. Rose Bradford found only 12 cases of pneumothorax in 500 patients with wounds of the chest, and in only 5 was its presence proved. Hale White found only 2 cases of air in the pleural cavity in the 50 cases seen by him in England. Naturally the amount of air that escapes is very small if the missile be a high velocity bullet from a rifle or machine gun, and consequently is overlooked unless carefully examined for within forty-eight hours or so after the reception of the wound. Further, of course, there is seldom if ever a valvular opening such as one sees in a pneumothorax due to tuberculosis. As shown in several autopsies of the infected hemothorax group there is at once a sealing of the opening in the lung substance by fibrin, which effectually prevents further escape of air. In 1 case the fibrinous plug had been inflated like a small balloon by the air in its attempt to escape from the damaged lung. Lastly, Osler,[11] has pointed out that the metallic phenomena which are the most striking signs of air in the chest, are best heard in cases with a consolidated lung and thickened pleura. Distention, immobility, lack of vocal fremitus, hyperresonance, absence of breath sounds and displacement of viscera are the signs of a pure pneumothorax, and can readily be confounded with those signs of an extensive effusion.

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[9] Loc. cit.

[10] Med. and Surg. Hist. of War of Rebellion, Pt. I, vol. ii, 623.

[11] Practice of Medicine: 8th edition, 1912, 671.

Lobar pneumonia was present in 4 cases, all four being on the side opposite to the wound and the subsequent hemothorax. These 4 cases together with the two mentioned in Group II give a total of 6 cases in our series in which all the physical signs and symptoms of a pneumonic infection existed in the side opposite to the injury. While trauma is a well-recognized cause of pneumonia since the days of Litten, who found a history of it in 4.45 per cent., I can find no mention in the current text-books and monographs of the opposite lung being involved. It is difficult to understand the pathogenesis of a pneumonia by "contre-coup." Rose Bradford noted that the hemothorax and pneumothorax might be found in the side opposite to the wound in the chest when the bullet penetrated the lung transversely. He noted that contralateral pleurisy was commoner in the cases infected with streptococci; he further admits that pneumonic consolidation does occasionally occur in the contralateral lung[12] but never in the side of the hemothorax.

A secondary hemorrhage into the pleural cavity is an exceedingly rare event if the patient be kept completely at rest for several days after his injury. In some cases it is said to have been the cause of death when attempting to transport the patient to the base too early. In 100 autopsies reported by Henry[13] death was due to hemorrhage in only 8.

Private D. J. B., Reg. No. 16691, was admitted to our care forty-eight hours after receiving a shrapnel wound of the right chest in the third interspace anteriorly. On admission, in addition to signs of a moderate hemothorax, there were undoubted evidences of pneumothorax; four days later, during which time he had been kept strictly at rest, he became extremely pale, the pulse became very rapid and thready, and the respiration became more rapid and labored. The diagnosis lay between a virulent infection of the hemothorax, as described by us above, or a secondary hemorrhage. The whole picture was more suggestive of the latter. However, to make certain, an exploratory needle was introduced and a few cubic centimeters of blood which clotted in the syringe were removed. That the blood was clotted was proof of the recent occurrence of the hemorrhage, as the bloody exudate usually removed by aspiration or drainage shows little or no clotting *in vitro*. Further the smears and cultures were negative and the patient gradually recovered with merely supportive treatment and absolute rest.

A case of cholohemothorax has been reported by Elliott and Henry[14] from a fistula between the liver and pleura following a bullet wound.

In 3 cases there was a simple fibrinous *pericarditis*, as evidenced by the presence of a pericardial friction. In 2 of these cases the wound was in the left chest. In another patient who had received a gunshot wound of the chest, the bullet having entered at the left nipple and passed out at the right nipple, there were signs of fluid (namely, a triangular area of absolute cardiac dulness and distant heart sounds), with the subsequent development of a to-and-fro pericardial friction, all of which were very suggestive of a hemopericardium.

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[12] J. Rose Bradford and T. R. Elliott, Brit. Jour. Surg., 1915, iii, 247.

[13] Brit. Med. Jour., 1915, ii, 130.

[14] Ibid., 1916, i, 9.

In still another case there were the characteristic signs of a *pneumopericardium*. As I hope to report the case at some length in the near future, suffice it to say that the patient received a shell wound of the lower left posterior aspect of the chest; the missile must have penetrated the diaphragm as well as the pleura, with the production of a subdiaphragmatic abscess. Two weeks after the receipt of the wound he developed sudden dyspnea, rapid pulse, precordial tympany, absence of heart sounds, and the presence of a most remarkable to-and-fro churning, musical, echoing sound synchronous with the systole and diastole of the heart, and persisting upon holding the breath. Some days later, after the air was absorbed, a dry pericardial rub became audible.

Twelve cases were complicated by extensive *infection* of the tissues from wounds for the most part other than those about the chest. In 2 cases the patient nearly succumbed to a secondary hemorrhage from the invasion of one of the main arteries of the upper or lower extremity. The case of the subdiaphragmatic abscess has already been referred to.

TREATMENT. In the majority (70 per cent.) of the cases apart from absolute bed rest and a bland nutritious diet no treatment was necessary, the bloody exudate being absorbed usually at the end of fourteen days after the reception of the wound. In 3 cases, in spite of the presence of signs at the expiration of two weeks, an exploratory aspiration was negative. In 5 other cases an exploratory aspiration revealed sterile bloody fluid, but the withdrawal of a few cubic centimeters sufficed to promote absorption. In another 5 cases amounts varying from 400 to 1600 c.c. were removed. This fluid was withdrawn slowly by means of an ordinary Potain aspirator without causing any outward symptoms. It never reaccumulated. The fluid itself varied in color from an ordinary deep scarlet to a deep chocolate; it was usually thin but sometimes of a syrupy consistence, and on standing showed little or no clotting. Only in one instance was an appreciable amount of fibrin noted. The postmortem examination of one case in the setrile and in several of the infected cases readily explains the absence of clotting *in vitro*, as the visceral and parietal pleuræ were covered by thick fibrin which had evidently separated out *in vivo*. This fibrin not infrequently plugs the lumen of the needle unless a large one (preferably a trocar) be used. Upon standing a sediment of red cells in various stages of decomposition with an occasional leukocyte can be found.

Henry[15] believes that primary coagulation of the effused blood and a deposition of fibrin occur in a few hours; afterward exudation of lymph may occur which will induce secondary clotting. Denny and Minot[16] offer experimental proof that the blood remains fluid in the pleural cavity not because of any alteration of its elements but because of previous coagulation and defibrination. Following the suggestion of Colonel Sir John Rose Bradford, two cases of extensive simple hemothorax were treated by aspiration and oxygen replacement. We used a simple home-made manometer and the oxygen tank of the Clarke oxygen-ether apparatus, introducing two needles into the chest, one for aspiration and one for the oxygen to enter. An attempt was made to keep a constant pressure equal to that noted before the withdrawal of any fluid. Of course, the resultant pneumothorax persisted for two or three days, and then gradually disappeared. We see no reason why all cases could not be aspirated if this procedure be used early (let us say on the sixth or seventh day) without giving rise to secondary hemorrhage, as was experienced by the physicians of the Royal Army Medical Corps in the South African War.

PROGNOSIS. Of the 87 cases only 6 died (69 per cent.), and of these 6 cases 4 were infected hemothorax, 1 died as the result of multiple amebic abscesses of the liver with local peritonitis, and 1 from an infected bullet tract in the lung. That is to say, approximately 8 per cent. of our hemothorax series died, which approximates very closely the mortality of Rose Bradford's series. In the latter's series of about 450 cases 10 per cent. died from sepsis, 5 per cent. from hemorrhage, and others from sundry complications.

In our series 69 were discharged well (79.3 per cent.), 11 improved (12.6 per cent) and on the high road to recovery; 1 was sent to England unimproved because of a coexisting paraplegia of the lower extremities. These encouraging figures, of course, hold true for only those cases which are removed from the battle-field and are eventually evacuated to the base. Many wounds of the chest must be fatal within a short time. As to what is the proportion of these we have as yet no figures to guide us. The ultimate prognosis of wounds of the chest, according to Hale White, seems to be good, for it is not uncommon to see such cases returned to the firing line. Convalescence is necessarily slow, but the flattening of the chest almost disappears in the course of several months.

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[15] Loc. cit.

[16] Amer. Jour. Physiol., 1916, xxxix, No. 4.